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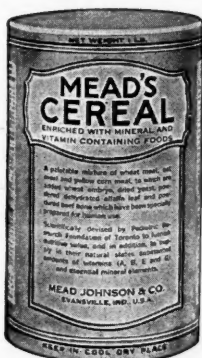
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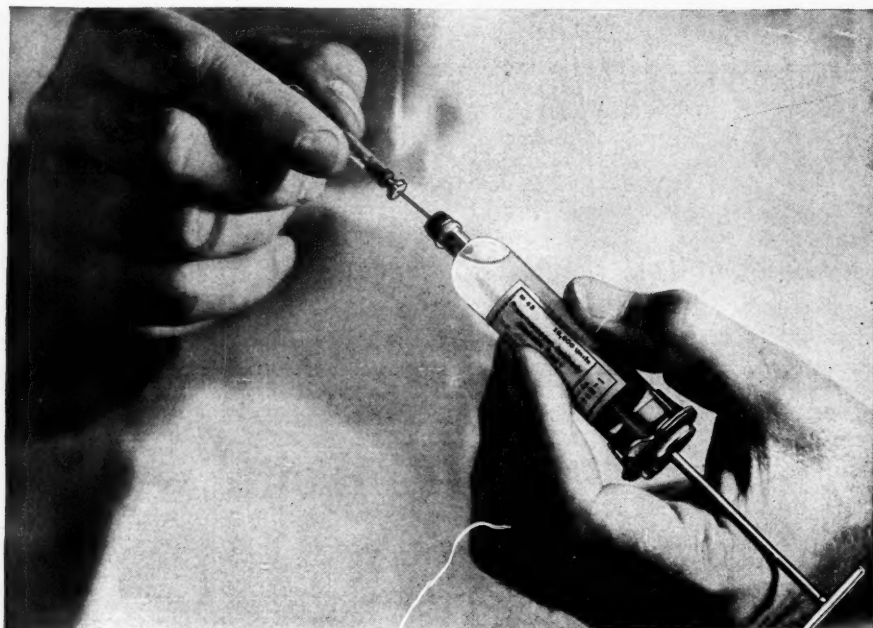
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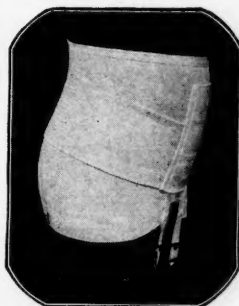
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ORIGINAL ARTICLES

OBSERVATIONS ON SERUM THERAPY*

FRANCIS G. BLAKE, M.D.

*(From the Department of Internal Medicine,
Yale University School of Medicine)*

When your president so graciously invited me to address you on the subject of serum therapy, it was at once apparent that I must limit my remarks to but a few aspects of so broad a field. I have chosen, therefore, to discuss first, certain theoretical considerations underlying the use of immune serum; next, to touch upon the methods available for the evaluation of serum therapy; and, finally, to say a few words concerning some practical points in the clinical application of serum therapy, which seem to me to deserve emphasis.

The intelligent development and application of a specific serum for the prevention and treatment of an infectious disease demands an understanding of the pathogenesis of the disease in question and a knowledge of the mechanism by which the host resists the infection or, if infected, brings about a natural termination of the disease. In general, the commoner and more important infectious diseases may be tentatively classified into three main groups with regard to mode of pathogenesis and perhaps with respect to mechanism of recovery.

The first and simplest situation is that in which the focus of infection is a local one at the site of which there is elaborated a potent soluble toxin. The essential and important damage to the host is caused by the injurious action of this toxin on particular tissues, the local lesion ordinarily being relatively unimportant unless it becomes so because of its anatomical location. The mechanism of recovery is, in large part, at least, through the elaboration of a neutralizing antitoxin by the host.

Diphtheria, tetanus, and scarlet fever, in so far as its toxic phase is concerned, fall into this group. The prevention of these diseases can be readily accomplished by passive immunization with the

appropriate antitoxin following exposure to the infection. On the other hand, the therapeutic use of antitoxin in these three conditions is not attended by equally successful results. As is well recognized, antitoxin therapy is highly successful in diphtheria; up to the present somewhat less so, though perhaps not of necessity, in scarlet fever; and of relatively limited and debatable value in tetanus. Why should these differences exist? The answer, I believe, is relatively simple and would appear to reside in the fact that certain practical and important differences occur in these three diseases.

In diphtheria the initial local lesion is symptomatic and ordinarily easily visible and readily diagnosed for a definite, even though brief period, before sufficient toxin has been absorbed to cause irreparable damage, the only major difficulty encountered being in the laryngeal form in which sufficiently early diagnosis may be difficult and in which anatomical rather than toxic factors may play the dominant role. In tetanus, on the other hand, the first clinical manifestation of the disease is not at the site of infection, but is due to the action of the toxin on the central nervous system. In other words, the important injury has already occurred before the disease can be recognized, and antitoxin therapy can at best accomplish no more than the prevention of further damage. In scarlet fever a still different problem is encountered, for the hemolytic streptococcus, in contradistinction to the bacilli of diphtheria and tetanus, possesses not only a toxigenic mechanism for damaging the host but also invasive and pyogenic properties, as is evident from the wide variety of focal and generalized septic processes such as sinusitis, otitis media, mastoiditis, meningitis, adenitis and pyemia, often caused by this organism in patients with scarlet fever. This septic phase of scarlet fever, as is well known, may begin early in the course of scarlet fever and dominate the picture. Furthermore, the natural mechanism of recovery from the septic phase of the disease, though conveniently described under the term antibacterial immunity, is in reality but vaguely understood at the present time. While it seems well established that the toxic phenomena of scarlet fever can be promptly cured by an adequate dose of antitoxin, and equally well estab-

*Read before the Rhode Island Medical Society, June 2d, 1932.

lished that antitoxin is of no demonstrable value in late septic conditions after the toxic or exanthematous stage has passed, there remains the debatable question of the value of early antitoxin therapy in preventing the development of septic complications and of beneficially affecting them, if they are already present during the early toxic stage.

The second group of diseases consists of those infections, bacterial in origin, in which more or less focal inflammatory lesions develop at the site of invasion and growth of the microbic incitants. Invasion of the blood, with bacteremia and generalized infection may or may not occur. Accompanying this process are the general phenomena of infection often described under the term general toxemia. The mechanism of the injury to the host, apart from the local anatomical lesions and the physiological disturbances resulting from them, though attributed by Pfeiffer to endotoxins, by Friedberger to anaphylotoxins, by Vaughan to non-specific toxic cleavage products derived from bacterial protein, and by many, particularly at present, to bacterial allergy or hypersensitiveness, are in fact but little understood. Similarly, the natural mechanisms of recovery, though often attributed to various humoral antibodies such as agglutinins, precipitins, opsonins, protective bodies, etc., acting with or without the cellular defensive mechanisms exhibited in the phenomenon of phagocytosis, are still somewhat obscure. Nevertheless, an antibacterial immunity, whatever its exact mechanism, must develop in response to infections of this group, since recovery does occur, and it should be emphasized that most of the available evidence points to the probability that the mechanism of recovery is not a simple humoral affair, as in the neutralization of a toxin by an antitoxin, but is presumably a co-operative enterprise between humoral antibodies and phagocytic cells. If this be true, only part of the curative mechanism can be supplied by a therapeutic serum; the other or cellular part must still be active and functioning in the host, if recovery is to be brought about by serum therapy.

This group of diseases, to mention only a few in which serum therapy is being more or less widely used, is represented by meningococcal meningitis, pneumococcal pneumonia, the pyogenic and septic hemolytic streptococcal infections, among which I would include erysipelas as well as the septic phase of scarlet fever. It will at once be recognized that the results of serum therapy in this group, though apparently of value in many instances, do not, as

yet, measure up to those obtained in diphtheria. Is this because the sera are lacking in proper antibodies or potency or because the cellular defenses of the host fail to co-operate, either through lack of complement or because the phagocytic cells have been too severely damaged by the toxic products of the infection? These questions are still to be answered.

The third group of diseases consists of those in which the microbic incitants are apparently obligatory intracellular parasites so far as present evidence goes. In this group fall many of the filtrable virus infections such as smallpox, chickenpox, yellow fever, measles, and presumably mumps and poliomyelitis. In addition, it seems not improbable that infections due to rickettsia—typhus and Rocky Mountain spotted fever—should be included here. Theoretically an immune serum should be of preventive value in these diseases, presumably by protecting the cells from invasion by the parasite, and such has proved to be the case, certainly in measles, chickenpox and mumps, in which the administration of convalescent immune serum after exposure effectively prevents the development of the disease. The same is true of other diseases in this group, at least experimentally in animals.

On the other hand, it would theoretically seem probable that immune serum should be of very little, if any, therapeutic value in the diseases of this group, since the serum would not be administered until after the parasite had invaded and damaged the cells of the body, a situation comparable in many respects to that encountered in tetanus, except that in the latter condition the injurious agent is a toxin rather than a living virus. I believe it fair to state that up to the present time the facts observed are in harmony with the theory, and that no serum, either artificial or convalescent, is of demonstrated therapeutic value in this group of diseases in man.

Let us turn now to a brief consideration of the criteria upon which the evaluation of the usefulness of a serum may be based. In general they are three in number: first, general clinical impressions based on experience; second, detailed and careful objective measurements of phenomena manifested by the sick individual, both before and after serum treatment; third, statistical data bearing on the duration of the illness, the incidence of complications and the mortality, in serum treated and control cases.

Theoretically the last or statistical method should

provide the most exact proof and be the method of choice. Practically it is usually fraught with almost insurmountable difficulties because of the numerous variables involved in nearly all infectious diseases, such as differences in severity, complications and mortality at different age periods, during different years, during different seasons of the same year and during different phases of a given epidemic outbreak, not to mention the further variables involved in the administration of serum with respect to time, method and dosage. Adequate statistical proof in the mathematical sense not only must include alternate, unselected, treated and untreated cases, but also must take into account the numerous variables involved, a few of which have been mentioned. How rarely these criteria are met one need not stop to emphasize. When every effort is made to meet these demands, the total number of cases to be analyzed, even in a large series, usually becomes subdivided into such small groups that the opportunity for error is sufficiently great to cast serious doubt upon or even to invalidate the results.

The second method of evaluation, i. e., objective observations of measurable phenomena,—such as a critical fall of temperature and pulse rate to normal, the prompt subsidence and disappearance of a visible lesion like the membrane in diphtheria or the rash in scarlet fever, sterilization of the blood in bacteremia or of the spinal fluid in meningitis and many others,—this method is relatively easy to carry out and has been widely and, I believe, profitably used. The obvious difficulty is not in the observations themselves but in their interpretation. Did the changes recorded follow as a result of serum therapy, or would they have occurred without it? To be acceptable, the changes observed must be reasonably consistent under given circumstances and the evidence convincing that they would not have occurred without serum. Otherwise we are driven back to the statistical method.

The first method, that of general clinical impression, is perhaps the one of least, yet not without some, value. Its obvious difficulty lies in the almost general human frailty of wishful thinking, which may lead to the advocacy of a serum when the therapeutic application is technically easy and apparent cure is almost sure to follow because that is the usual course of the disease, or, on the other hand, may result in resistance to the use of a serum when its application is technically more difficult

and time consuming and cure is not so certain to follow.

In discussing the practical applications of serum therapy, I do not propose to present a mass of statistical data or experimental observations, but rather to emphasize with illustrations certain practical points which I have come to believe are important. Furthermore, I shall not endeavor to cover all diseases in which serum may be used, but shall limit my remarks to certain diseases with which I have had a wider experience.

The first and, I believe, the most important factor in the successful use of serum is *time*. It may seem trite to say that the earlier the treatment is given the better will be the result, but I shall go even further and say that only when serum is given at the earliest possible moment are the best results to be obtained. In certain diseases, serum to be useful must be given before the disease develops and as soon as possible after exposure. Tetanus provides a useful example. The effectiveness of tetanus antitoxin as a preventive is too well established and too familiar to detain us. It must be used at once whenever the circumstances attending a wound indicate the possibility that tetanus may develop. These circumstances you know. Is it effective in curing the disease? Mr. Huntington, one of our students at Yale Medical School, has recently reviewed all the cases of tetanus in the records of a number of large hospitals in Boston, New Haven, New York, Philadelphia and Baltimore, over 600 cases in all. In only one group does the statistical analysis indicate a possible benefit from antitoxin treatment,—namely, those admitted on the first day of the disease and immediately treated intrathecally. Even under these circumstances the results in favor of serum therapy are only two times the standard deviation and statistically they should be three times to be certainly significant. Immediate intrathecal treatment would appear to be urgent and necessary if any benefit is to be secured.

Other diseases in which serum, to be useful, must be given before onset are measles, chicken-pox and mumps. Convalescent serum must be given within the first few days after exposure in order to prevent these diseases. The indications for prevention are existing illness in the exposed person or to prevent institutional outbreaks. Serum has no therapeutic value. In measles, in general, it is better to give half the preventive dose not later than the fourth day after exposure. Under these circum-

stances the child will usually have a mild attack and develop a permanent immunity.

In other diseases, successful results are attained by prompt treatment early after the onset of the infection. The importance of the time element in diphtheria is well known. An analysis of the 33 fatal cases of diphtheria at the New Haven Hospital during the last eight years shows that in 23 of them a physician was not called until the third day in 3, until the fourth day in 6, until the fifth day in 9, until the sixth day in 5, due either to ignorance or poverty in 20 instances, to religion—Christian Science—in 3. Of the remaining 10 cases, 4 were first seen by their physicians on the day of onset, 6 on the second day. Antitoxin was not given until the sixth day in 2, until the fifth day in 1, until the fourth day in 3, until the third day in 3. The one remaining case was a severe laryngeal diphtheria in a small infant treated on the second day, but dying because of respiratory obstruction rather than from the effects of the toxin. The difference between the results of early and delayed treatment in severe pharyngeal diphtheria is illustrated in Fig. 1. Again, immediate treatment is urgent and necessary; delay may be fatal.

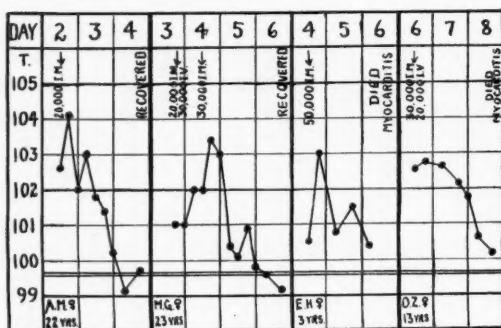


FIG. 1

FIG. 1.—Comparison of early and late antitoxin therapy in severe pharyngeal diphtheria. I.M. = intramuscular, I.V. = intravenous.

In scarlet fever it would appear evident that time is here, too, an equally important factor in the successful use of antitoxin. From the Fall of 1923, when the use of scarlatinal antitoxin was begun at the New Haven Hospital, until January 1932, 775 patients with scarlet fever were admitted. During this period only one of 246 patients treated on or before the third day of the disease died, the one exception being a woman of 22 with puerperal

scarlet fever admitted late on the third day with general peritonitis. On the other hand, 9 cases admitted and treated between the fifth and eleventh days, and 17 cases not treated, usually because admitted too late, died. The almost invariable result to be expected with early adequate treatment in predominantly toxic cases, in our experience, is illustrated by Fig. 2. Early treatment is urgent if the best results are to be obtained; delay may be fatal.

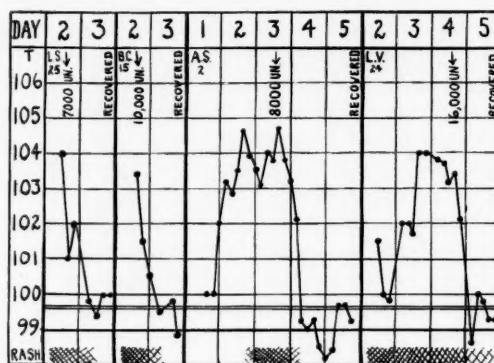


FIG. 2

FIG. 2.—Curative effect of antitoxin in early toxic scarlet fever.

The need for early treatment in lobar pneumonia has been stressed by many writers^{1 2} on the subject. For the most part, only in cases treated on or before the third day do the statistical studies presented in the literature show a convincing reduction in mortality. A comparison of early and late treatment is presented in Figs. 3 and 4 in patients with pneumococcus Type I and pneumococcus Type II pneumonia treated intravenously with Felton's refined pneumococcus antibody. Let me call attention to the presumably failing cellular defense suggested by the low leukocytic counts in the two cases treated late in the disease. One hardly need state that these are, of course, selected illustrations presented to emphasize the need for early treatment. As is well known, not all cases treated early respond so brilliantly, and obviously not all cases in which treatment has been delayed succumb.

With respect to the septic aspects of scarlet fever, early treatment offers the same advantages in our experience. Of 220 mild, nonseptic cases, untreated with antitoxin, 26.6% developed complications; of 53 treated with antitoxin, only 7.5%. Of 48 moderately severe nonseptic cases not treated, 64.5%

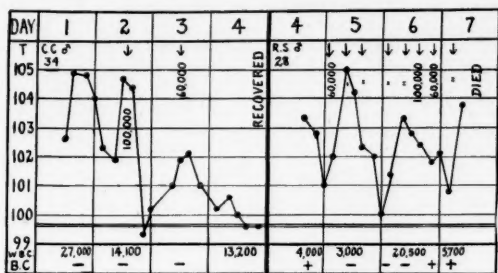


FIG. 3

FIG. 3.—Comparison of early and late treatment of pneumococcus Type I pneumonia with Felton's refined pneumococcus antibody. B.C. = blood culture.

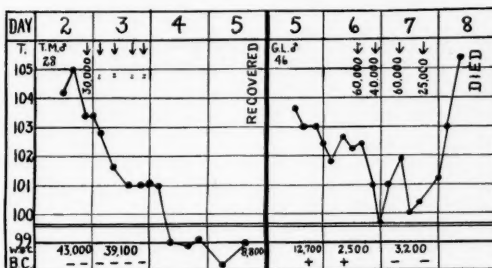


FIG. 4

FIG. 4.—Comparison of early and late treatment of pneumococcus Type II pneumonia with Felton's refined pneumococcus antibody. B.C. = blood culture.

developed complications; of 201 treated, only 15.9%. While our series is too limited to warrant any final conclusion, the differences are sufficiently great at least to suggest that early antitoxin treatment of scarlet fever is effective in causing a considerable reduction in the incidence of complications, a point of view supported by the more extensive studies of von Bormann.³

The therapeutic results in cases already complicated by pyogenic or septic conditions early in the disease will vary with the duration and nature of the septic process. Here again the time element would appear to be of the utmost importance. This is illustrated in Figs. 5 and 6.

In erysipelas we have been unable to obtain the satisfactory results with antitoxin treatment reported by Birkhaug,⁴ Symmers and Lewis,⁵ and others, nor do I believe that there is as yet satisfactory statistical evidence to support the therapeutic usefulness of this serum. In this I am quite in agreement with the views expressed by McCann.⁶ Furthermore, it would seem somewhat doubtful, in

view of the observations reported by Francis,⁷ whether Birkhaug's⁴ conception of erysipelas as a specific toxemia comparable to the toxic phase of scarlet fever is the correct one. To me, as set forth in more detail elsewhere,⁸ erysipelas would appear to be much more comparable to the septic than to the toxic phase of scarlatina. Certainly further work needs to be done on this problem before definite conclusions are justified.

Only one other matter relating to the practical application of serum therapy will be touched upon, namely, dosage. The first important point is to give the full amount of serum required in one dose whenever circumstances permit. This is easily pos-

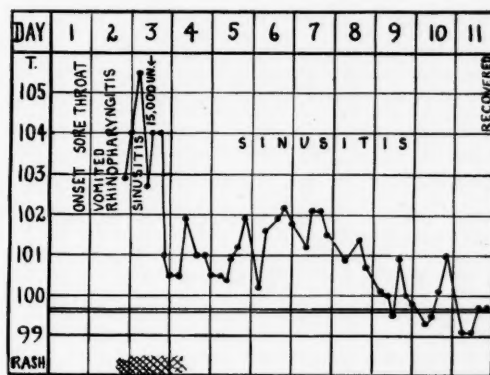


FIG. 5

FIG. 5.—Critical cure of toxic phase and gradual subsidence of sinusitis following antitoxin in toxic and septic scarlet fever. L. S., aged 21, severe.

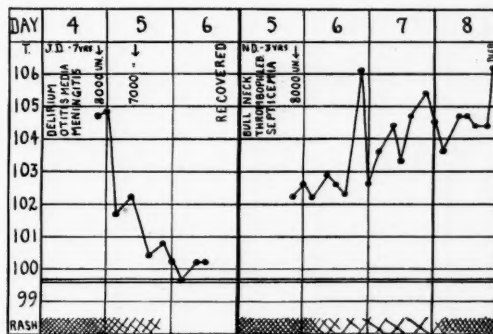


FIG. 6

FIG. 6.—J. D. Critical cure of toxic phase and rapid subsidence of otitis media and meningitis following antitoxin in extremely severe toxic and septic scarlet fever. N. D. Failure of late treatment with antitoxin in extremely septic scarlet fever.

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	Moderate	6000	8000
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Moderate purulent rhinopharyngitis and cervical adenitis	Moderate	12000	12000-16000
	Severe	12000-16000	16000-18000	6000-12000
	Extreme	16000-18000	18000-24000
Severe purulent rhinopharyngitis, sinusitis, severe cervical adenitis, otitis media, mastoiditis, ulcer- ative tonsillitis, sepsis, etc.	Severe	12000-16000	16000-20000	8000-16000
	Extreme	16000-24000	18000-30000

*One unit neutralizes 50 S. T. D. of toxin.

sible in diphtheria and scarlet fever. It is probably impractical in most instances in the treatment of lobar pneumonia, but there is ordinarily no reason why at least 60,000 units of the refined pneumococcus antibody should not be used in the initial dose, to be followed at four to eight hour intervals with subsequent doses as indicated. In meningococcus meningitis it is obviously impossible, since the volume to be given intrathecally is limited by anatomical considerations.

The second important point is to use a dosage sufficiently large to provide constantly some excess of antibodies above that required at the moment. It would ordinarily seem wiser to give a little more than may be necessary than to give too little, thereby permitting the infection to gain the upper hand again.

The problem of dosage will be illustrated only in the case of scarlet fever by the presentation of a table which has previously been published.⁹ Let me emphasize the necessity of using more than the minimum dose of 6000 units in most cases of scarlet fever deserving treatment, and point out the importance of noting the presence of purulent rhinopharyngitis as well as more obvious pyogenic and septic lesions, as an early indication of potential severity.

In conclusion, let me emphasize again that time is of the utmost importance in the successful application of serum to the prevention and treatment of infectious diseases. Until we as physicians look upon infectious disease as an urgent emergency requiring immediate action, just as the surgeon looks upon a perforated gastric ulcer as an emergency demanding immediate action, the best results will not be obtained and cannot be expected.

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CHRONIC MAXILLARY SINUSITIS AND ITS CLINICAL SIGNIFICANCE*

By BENJAMIN S. SHARP, M.D.
339 THAYER ST., PROVIDENCE, R. I.

In this survey of 85 cases, I shall attempt to outline the clinical significance of chronic infection of the maxillary sinuses.

Infection in the paranasal sinuses occurs rather frequently. The maxillary antrum is the most often affected and the probable cause is inadequate drainage. All the nasal sinuses are lined with a ciliated mucous membrane which is continuous with the nasal mucosa. It seems reasonable to assume that repeated infections of the nasal mucous membrane cause chronic inflammatory changes in the nasal accessory sinuses, particularly the maxillary antra. The ostia of the antra are placed above the floor of these sinuses, making drainage dependent in a great measure on the cilia of the lining epithelium.

*Read before the Rhode Island Medical Society, June 2, 1932.

We have observed a wide range of symptoms, both local and general, to which chronic sinus disease may give rise. The "common cold" or so-called "head cold" is a rather persistent complaint in this series. The acute infection of an antrum is ordinarily a very obvious process and tends to spontaneous recovery after running a course of seven to ten days; but, when local symptoms of a cold continue for months, sometimes with alternating remissions and exacerbations, it is almost a certainty that the cause is a chronic infection in the maxillary antrum.

Headache is a frequent symptom, either intermittent and neuralgic in character, simulating migraine, or just a sense of pressure about the eyes with dizziness when stooping over. At times the patient will have a jarring sensation in the teeth when walking down a flight of stairs. This referred pain or headache from chronic lesions, however, may affect only a single branch of the trigeminal nerve, and then show as infraorbital or supraorbital neuralgia, earache, pain in the eye, frontal headache, or similar symptoms.

Post-nasal discharge or "nasal catarrh" which causes cough and hawking especially in the morning is due usually to seepage from an edematous mucosa of the maxillary antrum. The following symptoms are considered in the same category: catarrh; dryness of the throat and nose; sensation of something in the throat, with a tickling or irritation; frequent clearing of the throat; a hawking to obtain a mass of tenacious, yellow, gummy material; hoarseness, with a dry unproductive cough; the morning "house cleaning" of the nasopharynx; bad breath; gagging and occasional vomiting.

The secretion from the post-nasal catarrh is an extremely important factor in producing respiratory disturbances such as tracheobronchitis, bronchiectasis and bronchial asthma. At times the sputum will be streaked with blood and the patient will exhibit signs of fatigue, malaise, anorexia, and loss of weight. Such a composite picture will even simulate pulmonary tuberculosis.

Gastrointestinal and eye disturbances are found in the younger patients, whereas auditory complaints, such as tinnitus aurium, vertigo and deafness, are observed in the middle-aged patients.

A long list of complications may be traced to the infected maxillary antrum, many pulmonary conditions, neuritis, myositis, arthritis, eye and ear affections, general lowering of vitality and resistance, digestive disturbances, impaired nutrition, loss of weight, anemia, general toxemia due to absorption in cases with much impediment to drainage, lethargy, convulsions and mental depression. Many cases have shown symptom complexes such as asthma, hayfever and hyperesthetic rhinitis.

At the time the clinical examinations are made, the objective findings vary greatly. The turbinates may be swollen, the mucosa may be more reddened in the affected nostril, and there may be pus in the meati. Again, the mucous membrane may be pale, thickened and water-logged in appearance, with no discharge in the meati or with a serosanguineous secretion present. Occasionally the turbinates may be dry, shrunken, pale and atrophic, with crusting. In many of the cases definite polyps have been noted within the nares. Usually we have found a lateral pharyngitis in most of our cases.

Transillumination gave us very little information regarding the antra. Not infrequently an antrum illuminated clearly, but when roentgenographed and when operated upon showed either a polypoidal or hyperplastic mucosa. Nevertheless, frank purulent cases usually could be recognized by a dark shadow over the malar eminence on transillumination.

Radiographic interpretation gave us our most definite and conclusive information in regard to the nature of bony walls, degree of thickening of the mucoperiosteum, and the size and shape of the maxillary sinuses. Therefore, deductions were drawn from our roentgenograms as to the presence or absence of disease in almost every case. These results were verified by clinical observations upon operation.

In regard to the roentgenographic examination, we cannot stress too greatly the importance of technically excellent films taken from proper angles of projection. We believe that most errors of interpretation are due to the tendency to be satisfied with films of poor quality.

The changes in the mucous membrane are of a chronic inflammatory character. There is an initial round-cell and serous infiltration followed by polypoid and cystic degeneration, periostitis and osteitis. The ciliated epithelium is desquamated, and metaplasia may be present. Many cases have exhibited acute pathology, as well as chronic inflammatory changes, on the same section of tissue.

In the following charts we have attempted to give a brief digest of all our cases, by age groups, but before showing them, we wish to explain briefly what is meant by the terms cured, improved, and unimproved.

By the term cured we mean that the case is free from systemic symptoms and complications for at least 18 months or over. Improved designates the patient is partially relieved of symptom complexes, and unimproved is self explanatory. There was one death in our entire series. This was due to acute meningitis and bronchopneumonia, with death five days after operation.

Age 1 to 20 years.							
Total Number of Cases 21							
General Symptoms:							
Running nose. Stiffness of nose. Nasal catarrh. Cough - with and without sputum. Headaches. Mucous and watery. Convulsions. Sore eyes. Itch. Conjunctivitis. Asthmatic attacks. Hoarseness.							
Tonsils and adenoids removed in all cases of this group.							
Clinical Examination.	No. of cases	Operation performed.	No. of cases	Operative findings.	Results	No. of cases	
					Minimum of 18 months after operation		
Turbinites	14	Antrostomy Antrostomy Window Caldwell-Luc	21	Pus present	21	Cured	14
Normal	0		11	This pus	15	Improved	7
Inflamed	14		1	Tenacious pus	8	Unimproved	0
Nasal findings	14		1	Polypoid Mucosa	19		
Normal	7			Cystic Mucosa	1		
Pus present	7			This and Necrotic	1		
Polyps present	0						
Comparative diagnosis procedures	Class			Microscopic Pathology			
	Class			Simple chronic inflammation.....	21		
				Otitis.....	2		
Transillumination	19			Tuberculous inflammation.....	0		
X-Ray interpretation	2						

Age 20 to 40 years.	
Total Number of Cases 22	

General symptoms:							
Post-nasal discharge. Running nose. Attacks of sneezing and watering. Headaches. Headaches. Cough and expectoration with blood streaked sputum. Cough with foul sputum. Foul odor to nostrils. Foul breath. Ticking sensation in throat. Hoarseness. Distress. Mucous. Watery. Loss of vitality. Trifacial neuralgia. Neuritis. Arthritis. Faint and attacks. Catarrhal deafness.							
Clinical Examination	No. of cases	Operation performed.	No. of cases	Operative findings.	Results	No. of cases	
					Minimum of 18 months after operation		
Turbinites	0	Antrostomy Antrostomy Window Caldwell-Luc	0	Pus present	42	Cured	27
Nasal	0		20	This pus	22	Improved	14
Inflamed	42		0	Tenacious pus	0	Unimproved	1
Nasal findings	42		0	Polypoid Mucosa	0		
Normal	0			Cystic Mucosa	0		
Pus present	42			This and Necrotic	14		
Polyps present	0						
Comparative diagnostic procedures	Class			Microscopic Pathology			
	Class			Simple chronic inflammation.....	42		
				Otitis.....	18		
				Tuberculous inflammation.....	1		
Transillumination	30						
X-Ray interpretation	0						

Age 40 and over.							
Total Number of cases 22							
General Symptoms:							
Headaches. Stiffness of nose. Headaches. Sensation of fullness in face. Unproductive cough. Attacks of sneezing and watery spells. Cough with foul sputum. Ticking sensation in throat. Loss of weight. Neuritis. Headache. Distress. Mucous. Attacks of fainting. Melancholy. Thymic pain. Sore eyes. Loss of hearing.							
Clinical Examination.	No. of cases	Operation performed.	No. of cases	Operative findings.	Results	No. of cases	
					Minimum of 18 months after operation		
Turbinites	0	Antrostomy Antrostomy Window Caldwell-Luc	0	Pus present	22	Cured	14
Normal	0		9	This pus	7	Improved	7
Inflamed	22		13	Tenacious pus	19	Unimproved	0
Nasal findings	0		0	Polypoid Mucosa	10	Dead	1
Normal	0			Cystic Mucosa	4		
Pus present	22			Mucosa	1		
Polyps present	14			Dentigerous cyst	1		
Comparative diagnostic procedures	Class			Microscopic Pathology			
	Class			Simple chronic inflammation.....	22		
				Otitis.....	19		
				Mucosa	1		
Transillumination	17			Dentigerous cyst	1		
X-ray interpretation	1						

In closing, we wish to state that the maxillary sinus is a very frequent focus for toxic infection. Numerous and bizarre complications are common. The objective clinical findings show considerable variations. Transillumination gave us very little

information regarding pathology or extent of the diseased process. Radiographic interpretation gave us the most definite and conclusive information in regard to the nature and extent of the pathology.

In this paper we are reporting our results of operative interference in eighty-five cases of chronic maxillary sinusitis, either unilateral or bilateral. Of this total, fifty-five cases we classify as cured, these patients presenting no systemic symptoms for at least eighteen months following the operative procedure. We report twenty-eight cases as improved, with partial relief of symptoms; one case unimproved, and one dead.

Surgical intervention was undertaken in all chronic cases as the only treatment offering some prospect of a cure or relief. We believe that patients suffering from severe systemic absorption or other serious complications from infected antra obtain their best chances of relief by a radical operation.

At this time I wish to extend my appreciation and gratitude to Dr. Harry Lee Barnes and his staff of Wallum Lake for their kind cooperation; also, to Dr. Simon Albert for his assistance in interpreting the X-ray films.

Discussion by Dr. Leech

With a paper as inclusive as Dr. Sharp's the discussant can hardly offer any new thoughts, and is almost limited, perforce, to emphasizing some of the essayist's points. In this connection, I would stress the importance of the anatomical formation of the antrum with its drainage opening at the top of the sinus as a factor in determining the vulnerability to infection of the antrum in contrast to those paranasal sinuses occupying the attic of the nose whose drainage canals tend to gravity drainage and earlier return to normal. Moreover, the antrum, situated as it is below these other sinuses, may act not unlike a catch-basin for the infection from above it. And not infrequently an acute fronto-ethmoidal infection may be succeeded by a long-standing antrum infection as a residual. In such cases, an accurate appreciation of the symptom—pain—is necessary, lest one be led astray, for the pain of chronic antrum disease is pre-eminently frontal rather than malar.

As Dr. Sharp has said, transillumination is of limited value, but the accessibility of the antrum to transillumination makes it at times, of help. However, too much dependence must not be placed upon transillumination or upon X-Ray as the sole arbiter in deciding upon sinus pathology.

While undoubtedly chronic sinusitis may act as a source of local infection elsewhere, I am not greatly impressed by the importance of that role, and in a list of focal infection sources the sinuses must be relegated to a position low in the percentage scale as compared with other sources.

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EDITORIALS

THE CATALOGUE FUND

The desirability of providing an up-to-date and usable catalogue of the books in our Medical Library has been pointed out in these columns many times, and it is with real pleasure that we note the beginning of a fund which will eventually make this possible. Contributions to date are as follows:

Dr. John W. Keefe \$100.00
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The proper cataloguing of the thirty thousand volumes which make up our library will cost between three and four thousand dollars, and the work will extend over three or four years. The funds thus far available, accordingly, simply provide a start, and it is hoped that every member of the Society who is interested in the library will make some contribution to further this essential work. Contributions should be sent to the Treas-

urer, Dr. Jesse E. Mowry, and should be marked "Catalogue Fund."

The JOURNAL is glad to endorse this effort to increase the value and usefulness of our Library.

PLEASE HELP

In the economic debacle of the last two years, perhaps no professional group has suffered more acutely than our colleagues in medicine—the graduate nurses.

Hundreds have been reduced to a minimal earning capacity. Many have had little or no employment and others have been forced to seek other methods of livelihood. There have been numerous cases of real destitution, as competent authorities will testify. Few doctors realize how serious has been this distress and fewer doctors have made any constructive effort or given serious thought towards a more equitable distribution of available nursing opportunities.

The nurses themselves with their usual courage and fortitude have done little complaining but have retained their professional poise which should command universal admiration. Serious investigation would bring out unbelievable acts of sacrifice and heroism among these distressed women in providing for their less fortunate associates.

But the moral of it all suggests that we physicians who are the means of employment to most of the nurses should distribute the work not alone for the efficiency to the patient, but with some thought to the necessity among the available nurses.

It would seem utterly unfair to give good cases and long cases to nurses married and living with employed husbands, while other nurses are in extreme need for themselves as well as dependent parents, brothers and sisters. Let's be thoughtful and wherever possible give work to the most needy of the nurses. Incidentally, we will discover some splendid, loyal, efficient nurses that we did not previously appreciate.

THE THIRD STAGE OF LABOR AND RETAINED PLACENTA*

PAUL APPLETON, M. D., F.A.C.S.
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The purpose of this paper is to stimulate interest in the better management of the third stage of labor,

with a view to lessening the complications that so frequently result from the poor management of this part of obstetrical practice.

One frequently observes obstetricians, well trained, conscientious, and skilful, go through the first and second stages of labor with conservative and painstaking attention, deliberate judgment, and excellent technical skill, only to fall down in the proper management of the third stage.

There are several probable causes for this imperfect placental stage delivery.

The attendant may be ignorant of the natural process which results in placental separation, or if cognizant of the facts, he may hurry to terminate the work, forgetting for the moment that uterine contraction and retraction must occur. He is prone to ignore his teaching of the histology and embryology of placental formation and the histological relation of the chorion frondosum to the decidua basalis, with the resultant relation of the villi to the uterine wall. He may not realize that placental separation and expulsion go on according to a definite mechanism just as well defined as the mechanism of the second stage of labor.

At this stage, the psychology of the attendant seems to go off on a tangent from his usual calculating logical mental process. The spectacular part of delivery is the birth of the child, whether spontaneous or operative. After that has been accomplished it is hard to realize that though less spectacular, the conduct of the third stage demands equal patience, equal judgment, equal observation and equal technique to the previous events of the accouchment. Hurry is the predominant fault, but hurry at this stage is extremely dangerous for it leads to ill-timed efforts at placental expulsion with the attending possibilities of hemorrhage, shock, and incomplete extrusion of the secundines.

During the third stage the watchfulness of the uterus and its contractions must of necessity be left to someone else while perineal repair is the primary event that is taking place. And the observation of uterine behavior at this time is a paramount responsibility. How often does the one to whom this is delegated show an intelligent interest and a keen observation in these phenomena?

Again, nine out of ten obstetricians, and ten out of ten occasional obstetricians pull on the cord.

*Read before the 121st Annual Meeting of the Rhode Island Medical Society, June 2, 1932, accompanied by motion pictures.

Delivery of the placenta by means of traction on the cord is at best a very dangerous procedure, and when this is done one is supplying an essential factor in the production of a tragic complication,—inversion of the uterus. I believe it is fair to say that inversion seldom occurs unless there has been traction on the cord.

In fact, even in our best clinics, truly normal placental delivery is a rapidly diminishing phenomenon, because so few recognize the *raison d'être* of the Crede manoeuvre, or wait until there is a real indication for its use.

What has already been said is not in a spirit of destructive criticism. No doubt we have all been guilty at one time or another of the faults enumerated and they are reviewed only with the intention of bringing out in bold relief those variations in management which one sees so often as to believe them correct.

Five-sixths of the bulk of the contents of a full term pregnant uterus is represented by the foetus. One-sixth constitutes the placenta and membranes. After the foetus is delivered, the involuntary uterine muscle contracts on its remaining contents. Each muscle fibre shortens. Thereafter, the normal muscle tone re-enacts the phenomenon of regular periods of contraction with intermittent periods of relaxation or rest. Usually the interval is as long as five to eight or ten minutes. After a few of these contractions have taken place, part of the placenta is squeezed away from its uterine attachment. In the Schultz mechanism, the center separates first, and blood from the uterine sinuses collects behind and forming a clot acts as a further stimulus to separation. This first bleeding is frequently invisible because it does not yet escape from the vagina. In the Duncan mechanism the edge of the placenta is first detached and the blood from the uterine sinuses trickles down through the cervix. As the rhythmic contractions recur, more and more of the placenta is separated, until it is entirely free and then the uterus shuts down hard and by a piston-like action forces the placenta into the vagina where it presents at the vulva.

Obviously this takes time. Usually from 15 to 30 minutes. It follows that any artificial attempt at forcing the separation by the Crede or any other method in less than one-half hour after the birth of the baby is a violation of nature's mechanism. It is more skilful to wait. It is vicious not to wait. The only valid reason to hurry the third stage is hemorrhage from the placental site, when the Duncan mechanism is going on. Hemorrhage from a torn cervix or a lacerated perineum is not a reason for hurrying the third stage. The source of the bleeding should be determined and dealt with in an appropriate rather than an empirical and possible erroneous manner. Shock due to prolonged or operative delivery is not an indication to hurry the third stage. It is rather a contra-indication. Attempts to Crede the uterus are painful and the addition of afferent painful stimuli will increase the shock. Should hemorrhage occur added to shock, one's patient is in double jeopardy.

It is wise in each case to study the signs of placental separation and be able to readily detect the fact that the placenta is detached and ready to be delivered. The most reliable signs are:

1. Spontaneous advancement of the cord without traction on it.
2. Dimpling of the fundus.
3. Antero-posterior flattening of the uterus due to the descent of the placenta and the compensatory contraction of the now empty fundus.
4. Fullness over the bladder due to the presence of the placenta in the lower uterine segment.

Last of all, after the secundines have been delivered they should be adequately and carefully inspected. This cannot be done by a glance even by the most experienced. It should not be left to a nurse. Proper inspection means laying the placenta out on a flat surface, and systematically going over first the foetal and then the maternal side in order to note the absence of fragments or tearing of the vessels, which is the cardinal sign of possible succenturiate placentae. In order to do this all clots must be carefully wiped away and the tissue subjected to minute and painstaking inspection.

After the placental delivery, the uterus should be either constantly held or frequently palpated, by someone who knows how to do it. Its condition should be under scrutiny for a full hour. If the uterus is in contraction no massage is necessary or desirable. On the contrary, it is then illogical. The same is true when the uterus is in the relaxed stage unless there is hemorrhage, either visible or concealed, but one must then be on the alert for contraction is highly desirable.

It is generally recognized the world over that either Ergot or Pituitrin or other oxytocics should not be administered before the placenta is delivered.

If given during the third stage, a contraction ring or an hour glass uterus may result with the placenta fully detached but retained and impossible of spontaneous extrusion.

I should like to reiterate that after the completion of the third stage of labor the patient should not be left for an hour. Few men have the obstetrical conscience to stay by for an hour, but are content to depend upon a nurse or someone less competent to complete their bounden duty. I feel perfectly justified in saying that anyone doing obstetrics who leaves his patient in less time, disregarding whether she is at home or in a hospital, is indeed ill fitted to practice an art so fraught with potential danger. Serious shock and appalling hemorrhage most often occurs, if it is going to, within the first hour post partum. Close attendance during this time is a professional obligation. To ignore it is a frank confession of incompetence.

Retained placenta is due either to failure of separation from its uterine attachment, usually due to histological causes, or failure of a properly separated placenta to be extruded from the uterus on account of premature contraction of the cervix or lower uterine segment.

There are two types of adherent placenta. The so-called placenta accreta is that in which the villi have branched so prolifically as to form an abnormally firm attachment to the decidua, whereby it does not and cannot detach by the simple mechanism of normal third stage uterine contraction.

If the villi have penetrated the decidua and burrowed deeply into the muscularis of the uterus with the same clinical result of failure of separation, the condition is known as placenta increta.

The main placenta mass may properly detach but an added pedunculated island or islands, the so-called Placenta Succenturiata, may remain behind and undelivered. This is diagnosed always by proper inspection of the foetal surface, noting the tearing of nutrient vessels, where the retained portion has remained behind.

Imperfect or inefficient or absent uterine contractions will naturally result in an absence of the onset in the normal mechanism of the separation. Such a condition may result from uterine muscle exhaustion or inertia due to a long or tedious labor or delivery, a difficult operative delivery, deep anesthesia, sepsis, intercurrent disease, or ruptured uterus.

Cervical spasm per se or induced by the premature use of oxytocics may result in retention of a completely separated afterbirth which cannot be expelled because of the reduced calibre of the contracted cervix.

The treatment of retained placenta from any cause is directed towards two methods of its delivery. External, by appropriate massage, i.e., the Crede manoeuvre; or internal, i.e., manual extraction.

The former is the first to be tried because it is the safest. Invasion of the uterus even under aseptic surroundings is a procedure fraught with danger of sepsis. The proper method of the Crede manoeuvre is to imitate as far as possible the forces of nature. If the contractile efforts of the uterus are present, the squeezing must be done only during a contraction, never during the resting stage. It consists of firm steady compression of the fundus manually through the abdominal wall, not a number of irregular unstudied squeezes. The pressure should be steady after the manner of pressure on the rubber bulb of a syringe, producing a piston-like action in the lower uterine segment.

Should the uterine muscle have lost its tone and fail to contract, the artificial pressure should be steady for a minute imitating the normal contraction, followed by a rest period of two or three minutes before another attempt. Several rhythmic attempts are safer and more effective than irregular manipulations with insufficient intervals of relaxation. Traction on the cord is to be *scrupulously avoided* because the Crede manipulation plus cord traction especially in the presence of an inert uterine muscle provides the necessary factors for uterine inversion, a most desperate situation. One should prefer to take his chances with manual extraction of a retained or adherent placenta rather than the slightest possibility of inversion of the uterus.

Manual removal is a last resort, but is preferable to violent irregular attempts to squeeze out the placenta from above. It means, of course, invasion of the entire parturient canal which presupposes an entirely fresh aseptic preparation of both the patient and operator. One cannot be too thorough about this to remove every controllable source of contamination and the fresh introduction of bacteria into a perfect nidus, the uterine mucosa.

With great care to prevent touching anything on the way, the folded gloved hand is introduced into

the vagina and thence to the cervix. One notes the condition of the cervix, dilating gently if necessary, and the hand enters the uterus. The cord as a guide is followed to its placental attachment and the placenta is then carefully explored around its margin to determine a beginning separation and a line of cleavage. Following this plane, with a back and forth sawing motion it is separated and collected in the hand, when it is drawn down deliberately in order to favor the peeling off of adherent membrane. Following such removal, oxytocics should be given and one must be especially vigilant in observation for possible hemorrhage. It is desirable to avoid, if possible, packing the uterus in order to allow free drainage as a mechanical bar to the retention of introduced bacteria. But in the presence of severe hemorrhage, packing should not be delayed. One must give individual consideration to the greatest danger that presents in the case in hand, selecting of course the lesser evil.

In conclusion, may I emphasize with vigor the desirability of a more careful conduct of the third stage of labor, invoking especially those cardinal obstetrical virtues, patience, individual study, logical deliberate judgment, based upon the natural mechanism of placental separation, painstaking inspection of all delivered material, and above all an aseptic conscience.

SOCIETIES

MEETING OF THE NEW ENGLAND DERMATOLOGICAL SOCIETY

The regular quarterly meeting of the New England Dermatological Society was held for the first time in Providence at the Rhode Island Hospital, Wednesday, October 19, 1932. At 3 P. M. over 45 members of the society from Boston, Worcester, Springfield, Brockton, New Haven, Hartford, Bridgeport, met at the Out-Patient Department, where 22 cases of unusual and rare skin diseases were exhibited by the local members of the dermatological staff.

Cases presented: Kaposi Sarcoma (Dr. Ryan), Syringomyelia (Dr. Ryan), Fragile and twisted hairs (Dr. Ronchese), Tubercular lymph scrotum and lymphangectases (Dr. Ronchese), Dermatitis and Carcinoma from X-rays (Dr. Ronchese),

Nevus Pigmentosus (Dr. Ryan), Pseudo-Xanthoma Elasticum (Dr. Ronchese), Squamous cell carcinoma of scalp (Dr. Ryan), Multiple benign basal celled epithelioma of the scalp (Dr. Ronchese), Psoriasiform lues (Dr. Ryan), Late cutaneous lues (Dr. Wilcox), Urticaria pigmentosa (Dr. Ryan), Bathing-suit type naevus (Dr. Ryan), Scleroderma, 2 cases (Dr. Wilcox), Kaposi Sarcoma (Dr. Cohen), Onychodystrophia (Dr. Abel), Alopecia Cicatrisata (Dr. Sawyer), Sporothricosis (Dr. Naddler of New Haven), Erythema Multiforme (Dr. Sawyer), Favus of the scalp (Dr. Cohen), Acne agminata (Dr. Cohen).

Then in the conference room of the Peters House the cases were discussed by Drs. Lane, Burns, Towle, McCarthy, Smith, Greenwood, Boardman, Blaisdell, Downing, Standish, Strauss, Cheever, Cummins, Swartz, and by the exhibitors.

Through the courtesy of the superintendent of the Rhode Island Hospital a buffet supper was served at the Peters House.

BOOK REVIEWS

"THE RIDDLE OF THE RHINE," by Victor Lefebure.

Published by E. P. Dutton & Company, New York.

Here is a book that the student of past and future wars will read with much interest and great profit.

From the time of the first German gas attack in April, 1915, the importance of chemical warfare increased so tremendously that by the summer of 1918 fully 50% of all German shells fired at the Allies were chemical shells. The gradual development of this type of warfare is admirably described. Along with its development we see the frantic efforts of the Allies to protect their troops and at the same time prepare to meet and beat the Germans at their own game. The author points out again and again the monumental task with which they were confronted—the research necessary—the laboratories needed and finally the huge and hastily built factories. All this is perhaps overemphasized to contrast it with the ease with which Germany turned the enormous chemical plants of the I. G. (Interessen Gemeinschaft) to making chlorine,

phosgene, mustard gas and the like. At the outbreak of the war, Germany held a virtual monopoly of the dye industry, and further the manufacture was in the hands of the I. G.

Since the base for the manufacture of war chemicals was the same as the base for the manufacture of dyes, it can be readily seen how easily the big plants of the I. G. could turn to supplying the German Army with the necessary gas and other chemicals.

Due to the Allied blockade Germany soon felt the want of raw material. Without nitrogen she would have had to give up the fight long before she did. Since her supply of nitrates from Chile was soon exhausted, she turned with characteristic resourcefulness to fixing nitrogen from the air in the big Haber process plants. These plants again were and are an integral part of the I. G. combine. Now in peace time they are the center of a big fertilizer industry but with the same inherent war time possibilities.

As to the future of chemical warfare. The author doubts very much if any number of Hague conventions or International agreements can outlaw it effectively. Any nation at bay will in the future as in the past hasten to adopt any method of fighting that gives hopes of success. He feels that war is a ghastly business at best and that chemical warfare is no more ghastly and no more inhuman than other methods. His figures if correct, and one cannot reasonably doubt them, show that though the casualties from gas were large in proportion to the total—the percentage of deaths was much smaller than in any other class of casualties.

The author's statement that American surgery was retarded from 50 to 75 years during the war by an acute shortage of novocaine, beta-eucaine and ether is certainly not true. We all know that though these substances may have been expensive and hard to come by, there was no acute shortage of any of them. In the main though he sticks to facts and stays on his own familiar ground.

The Riddle to be solved is what to do with Germany's chemical organization. Shall it be left intact to repeat in some future war what it did in the World War or shall it be crippled and ringed about with restrictions to hamper war activity in the future? Since the Treaty of Versailles ignored Germany's chemical activities—since many years have passed since the signing of the Treaty and all these plants are now an integral part of Germany's

peace time organization, it is much too late to include them in the general disarmament scheme. Much better for the world to solve the riddle by each great nation's making itself chemically independent of Germany.

This is the author's solution, and a perfectly logical one, all of us will agree. We can well hope that the propaganda put forth in "The Riddle of the Rhine" may bear fruit a hundred fold.

"EASIER MOTHERHOOD," by Constance L. Todd.

Published by The John Day Co.

Written as an effort by a laywoman to bring to the attention of womanhood that with available modern methods their childbearing need not be painful, or at least not excessively so; in the hope that by her careful study and presentation of the facts from the laywoman's point of view she might help to create a demand among women for more attention and care directed to the relief of pain during labor.

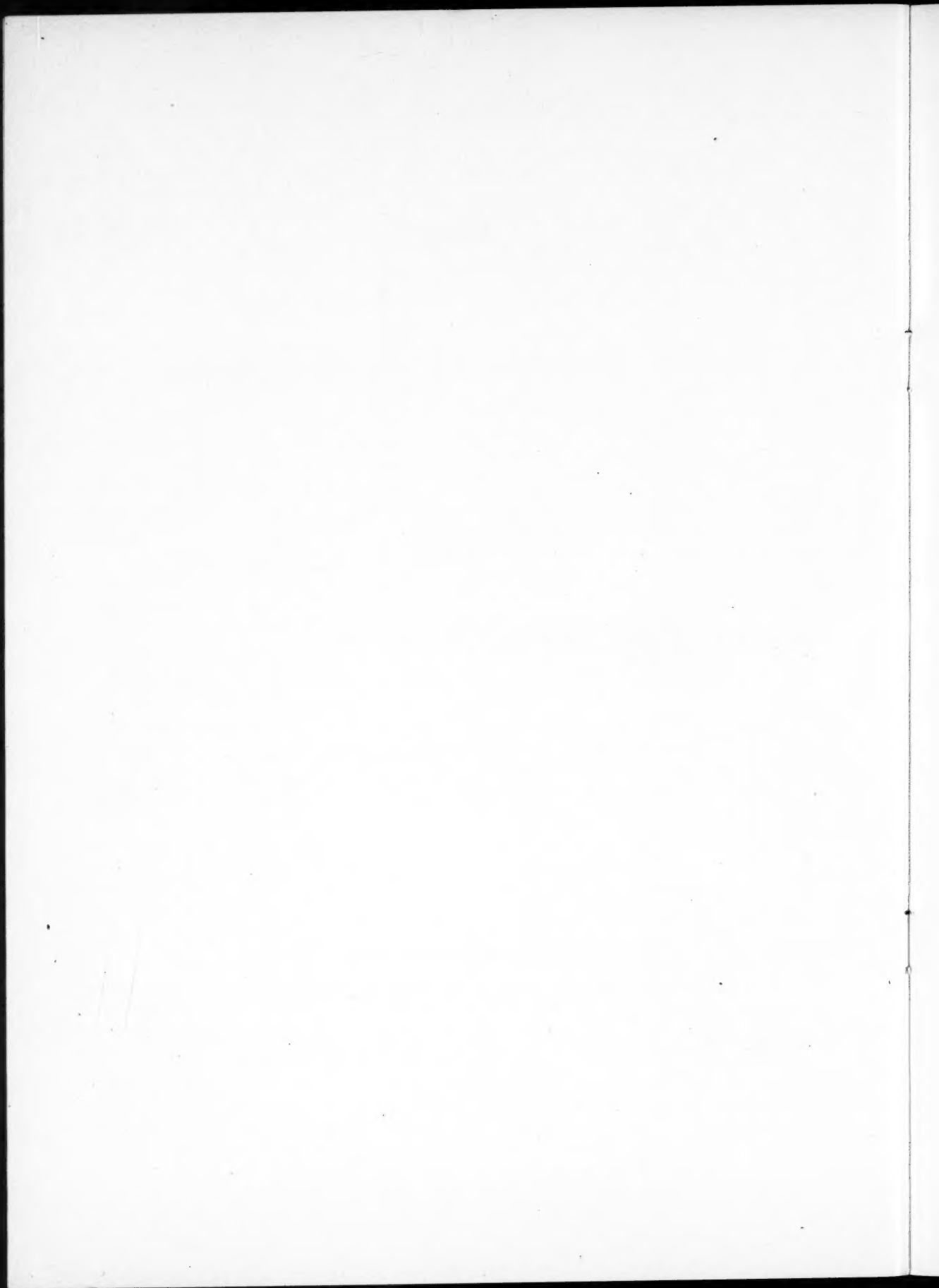
After decrying the old attitude toward pain in childbirth as something physiological and therefore necessary, as something which woman has inherited as part of the curse of Eve, therefore to be borne with patience, the author goes on to trace the movement toward alleviation of pain in labor which according to her study has reached its climax in the Gwathmey technic. In further chapters she traces the acceptance of the method giving numerous testimonials in its favor from cities all over the country, rather caustically criticising members of the profession in certain large centers for their lack of enthusiasm or their preference for methods of their own. On the whole one gets the idea that Miss Todd will be satisfied if the doctors will use at least some method of continuous pain alleviation but will be happy if they adopt her favorite Gwathmey technic.

The book on the whole is well and enthusiastically written. In so far as her lurid descriptions of the horrors to be expected in childbirth, and the cruelty and callousness to suffering to be found in some doctors, may drive women to insist on having the most relief possible and to be more careful in selecting their obstetrician, Miss Todd's book will do good: in so far as the same descriptions awake morbid fears, and by suggestion increase suffering beyond what is normal, in the neurotically inclined, her book will do harm.

The
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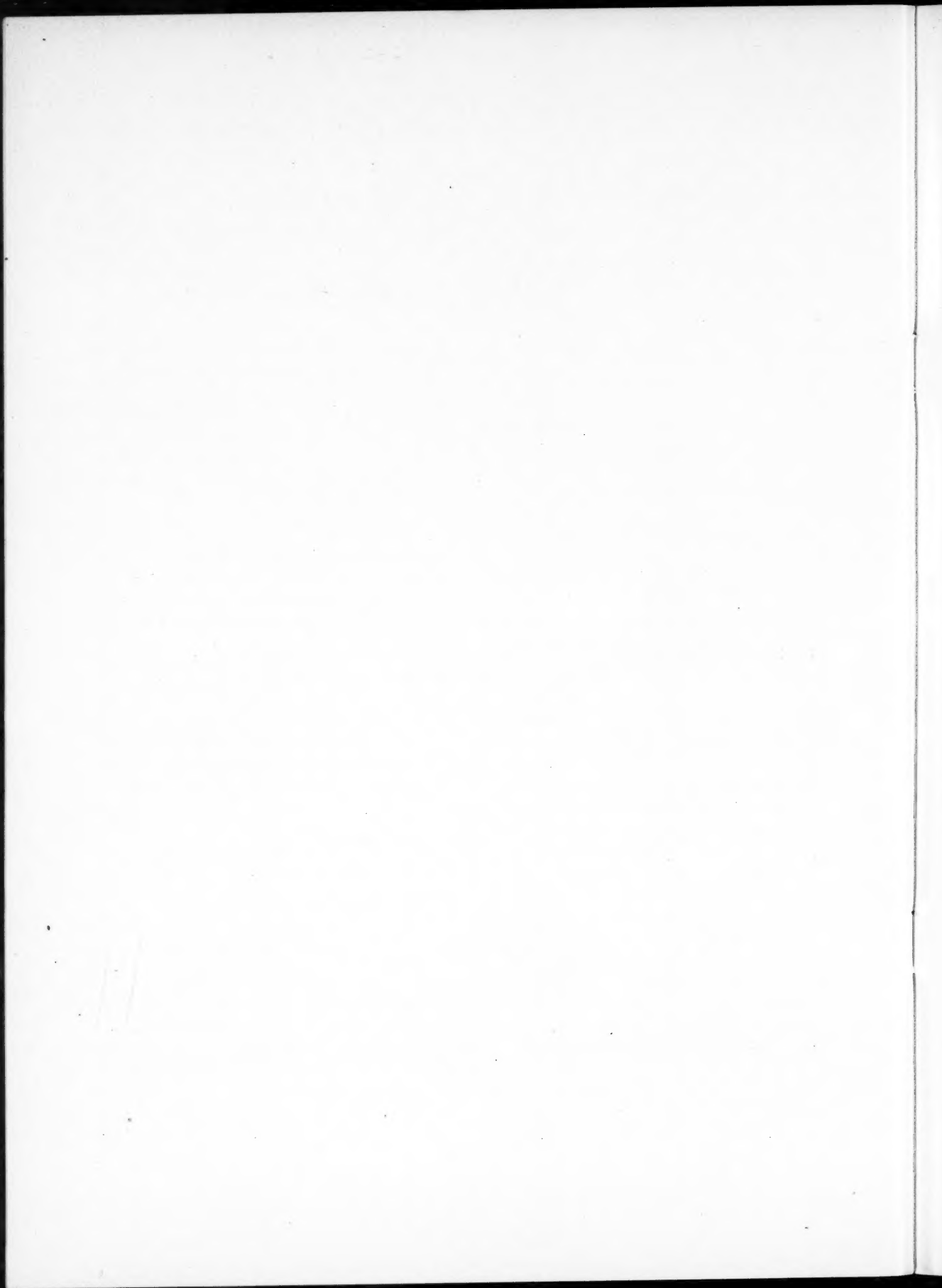
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85-86% protein, Knox Sparkling Gelatine is free from sugar, artificial coloring or flavoring. Thus Knox should be specified to avoid the thoughtless use by the patient of ready-mixed gelatin preparations which contain 70% or more sugar and acid flavoring. On request, the Knox Gelatine Laboratories, 436 Knox Ave., Johnstown, N. Y., will send you facts on Gelatine in the Diet, prepared by accredited authorities, and free diet recipe books to give to patients.



KNOX is the real GELATINE

BE SURE TO SPECIFY KNOX

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Gastric tissue juice extract, **ENZYMOL**, proves of consistent service in the treatment of pus cases.

ENZYMOL resolves necrotic tissue, exerts a reparative action, dissipates foul odors; a physiological, enzymic surface action. It does not invade healthy tissue; does not damage the skin.

The hydrolyzed material is readily removable by irrigation.

These are simply notes of clinical application during many years:

Abscess cavities
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Sinus cases
Corneal ulcer
Carbuncle
Rectal fistula

Diabetic gangrene
After removal of tonsils
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